PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 7 : C07D 253/06

A1

(11) International Publication Number: **WO 00/35888**

(43) International Publication Date: 22 June 2000 (22.06.00)

(21) International Application Number: PCT/IB99/01955

(22) International Filing Date: 7 December 1999 (07.12.99)

(30) Priority Data:
2171/CAL/98 14 December 1998 (14.12.98) IN

(71)(72) Applicant and Inventor: VYAS, Sharad, Kumar [IN/IN]; B/31, Goyal Park Apartment, Opposite Lad Society, Vastrapur, Ahmedabad 380015, Gujarat (IN).

(74) Agents: AHUJA, Sudhir, D. et al.; D.P. Ahuja & Co., 53, Syed Amir Ali Avenue, Calcutta 700019, West Bengal (IN).

(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published
With international search report.

(54) Title: AN IMPROVED PROCESS FOR THE PREPARATION OF 3,5–DIAMINO–6–(2,3–DICHLOROPHENYL)–1,2,4–TRIAZINE

(57) Abstract

There is disclosed an improved process for the preparation of 3,5–diamino–6–(2,3–dichlorophenyl)–1,2,4–triazine which process comprises the step of reacting 2,3–dichlorobenzoylchloride with cuprous cyanide in presence of acetonitrile and a cosolvent to produce dichlorobenzoyl cyanide said dichlorobenzoyl cyanide is reacted with aminoguanidine bicarbonate to produce an intermediate product, which is cyclized in presence of aqueous potassium hydroxide to produce 3,5–diamino–6–(2,3–dichlorophenyl)–1,2,4–triazine.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	**ES**	Spain	**LS**	Lesotho	**SI**	Slovenia
AM	Armenia	**FI**	Finland	**LT**	Lithuania	**SK**	Slovakia
AT	Austria	**FR**	France	**LU**	Luxembourg	**SN**	Senegal
AU	Australia	**GA**	Gabon	**LV**	Latvia	**SZ**	Swaziland
AZ	Azerbaijan	**GB**	United Kingdom	**MC**	Monaco	**TD**	Chad
BA	Bosnia and Herzegovina	**GE**	Georgia	**MD**	Republic of Moldova	**TG**	Togo
BB	Barbados	**GH**	Ghana	**MG**	Madagascar	**TJ**	Tajikistan
BE	Belgium	**GN**	Guinea	**MK**	The former Yugoslav Republic of Macedonia	**TM**	Turkmenistan
BF	Burkina Faso	**GR**	Greece			**TR**	Turkey
BG	Bulgaria	**HU**	Hungary	**ML**	Mali	**TT**	Trinidad and Tobago
BJ	Benin	**IE**	Ireland	**MN**	Mongolia	**UA**	Ukraine
BR	Brazil	**IL**	Israel	**MR**	Mauritania	**UG**	Uganda
BY	Belarus	**IS**	Iceland	**MW**	Malawi	**US**	United States of America
CA	Canada	**IT**	Italy	**MX**	Mexico	**UZ**	Uzbekistan
CF	Central African Republic	**JP**	Japan	**NE**	Niger	**VN**	Viet Nam
CG	Congo	**KE**	Kenya	**NL**	Netherlands	**YU**	Yugoslavia
CH	Switzerland	**KG**	Kyrgyzstan	**NO**	Norway	**ZW**	Zimbabwe
CI	Côte d'Ivoire	**KP**	Democratic People's Republic of Korea	**NZ**	New Zealand		
CM	Cameroon			**PL**	Poland		
CN	China	**KR**	Republic of Korea	**PT**	Portugal		
CU	Cuba	**KZ**	Kazakstan	**RO**	Romania		
CZ	Czech Republic	**LC**	Saint Lucia	**RU**	Russian Federation		
DE	Germany	**LI**	Liechtenstein	**SD**	Sudan		
DK	Denmark	**LK**	Sri Lanka	**SE**	Sweden		
EE	Estonia	**LR**	Liberia	**SG**	Singapore		

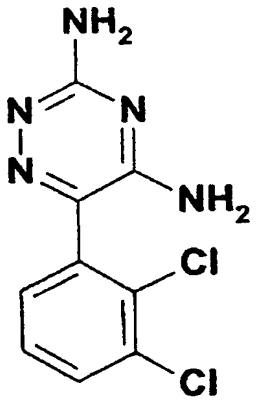
AN IMPROVED PROCESS FOR THE PREPARATION OF 3,5-DIAMINO-6-(2,3-DICHLOROPHENYL)-1,2,4-TRIAZINE

FIELD OF THE INVENTION

This invention relates to an improved and economical process for the preparation of 3,5-diamino-6-(2,3-dichlorophenyl)-1,2,4-triazine, which is also known as lamotrigine. This is a new structural class of antiepileptic drug.

BACKGROUND OF THE INVENTION

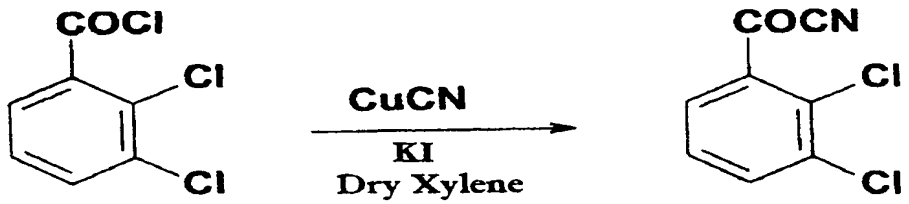
The need for a drug, which will be effective in the patients who do not satisfactorily respond to conventional antiepileptic drugs has always been there. Also, a selectivity of specific mechanism of action reduces the side effect burden as in the case with Lamotrigine i.e. 3,5-diamino-6-(2,3-dichlorophenyl)-1,2,4-triazine (I). Lamotrigine, the selective sodium channel blocker which inhibits synaptosomal excitatory neurotransmitter release, is a use and voltage dependent inhibitor of presynaptic sodium channels.



(I)

Lamotrigine can be prepared according to the literature procedure described in the U.S. patent 4602017 which comprises reacting 2,3-dichloro acyl chloride with cuprous cyanide and potassium iodide in dry xylene medium and reacting the resultant dichloro acyl cyanide with aminoguanidine bicarbonate and cyclizing the reaction product in presence of 10% methanolic KOH or n-propanol to produce lamotrigine.

In the US patent 4602017, acid chloride (II) (1 mole equivalent) was converted to acyl cyanide (III) (Reaction-1) by using metal cyanide viz. copper cyanide (~2.4 mole equivalent) and potassium iodide (~2.4 mole equivalent) in dry xylene (~20 vol./wt of acid chloride) as solvent.



(II) (III)

Reaction - 1

In the reaction of acid chloride (II) to acyl cyanide (III) as in the Reaction-1, the voluminous quantities of solvent dry xylene, demands the larger reactor size for comparatively smaller quantities of acid chloride.

Also, the use of potassium iodide increases the cost of the process. In the final step of cyclization, an alcoholic solvent i.e. alcoholic KOH further adds up to the cost.

The activation of copper cyanide by using metal iodide is certainly noteworthy.

However, taking into view the cost of metal iodide viz. potassium iodide, the subject invention looks into the possibility of avoiding the use of it, to reduce the manufacturing cost. Moreover, use of the solvent viz.dry xylene, in such a large quantities adds to the cost of the product.

SUMMARY OF THE INVENTION

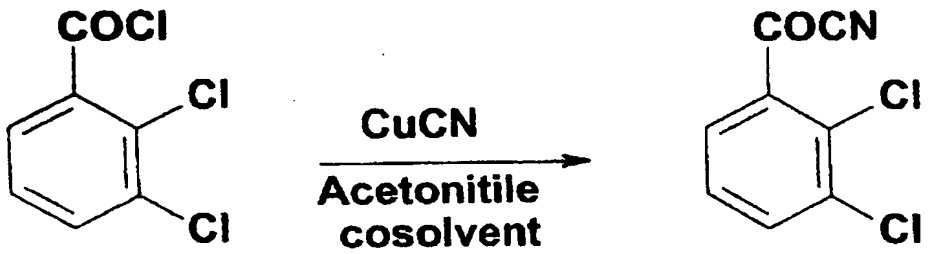
The object of the present invention is to provide a process for the preparation of lamotrigine which is cost effective.

Another object of the present invention is to provide a process for the preparation of lamotrigine which does not use potassium iodide, or alocoholic potassium hydroxide and requiring lesser amount of solvent like toluene or xylene which are used only as a cosolvent.

Yet another object of the invention is to provide a process for production of lamotrigine of high grade purity, highly satisfactory impurity profile, white in color, free flowing, having lower moisture content, which can be efficiently and effectively dried and can be easily converted into pharmaceutical compositions.

Accordingly the present invention provides an improved process for the preparation of 3,5-diamino-6-(2,3-dichlorophenyl)-1,2,4-triazine of formula I, which process comprising the steps of :

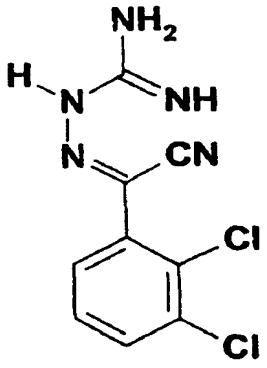
(a) reacting 2,3-dichlorobenzoyl-chloride (II) with cuprous cyanide in presence of acetonitrile and a cosolvent, to produce dichlorobenzoyl cyanide (III);



(II) (III)

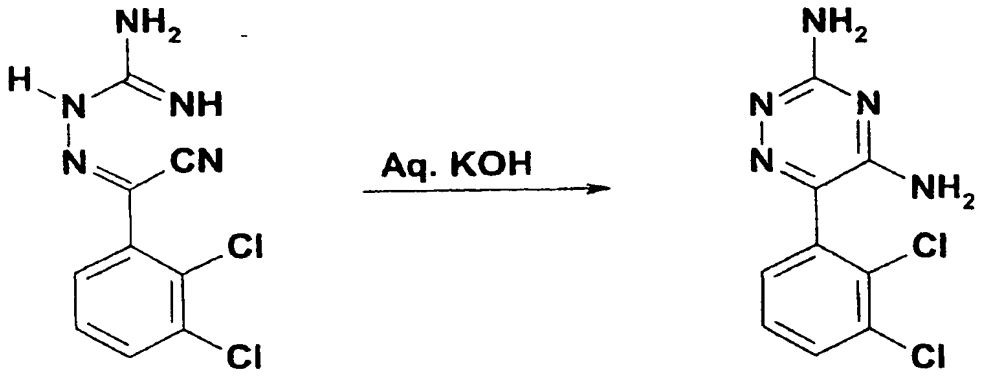
Reaction - 2

(b) reacting dichlorobenzoyl cyanide (III) obtained in step (a) with aminoguanidine bicarbonate to produce the intermediate product of formula (IV), and



(IV)

(c) cyclizing said intermediate of formula IV in presence of aqueous potassium hydroxide to produce 3,5-diamino-6-(2,3-dichlorophenyl)-1,2,4-triazine.



(IV) (I)

Reaction-3

DETAILED DESCRIPTION OF THE INVENTION

The present invention targeted towards lowering the cost of Lamotrigine provides an industrially economical process for the preparation of Lamotrigine i.e. 3,5-diamino-6-(2,3-dichlorophenyl)-1,2,4-triazine (I).

In the instant invention, 2,3-dichlorobenzoylchloride (II) is transformed into 2,3-dichlorobenzoyl cyanide (III), which is the building block for the heterocyclic ring, as shown in Reaction-2 above. Acetonitrile is used for complexation with copper cyanide. Copper cyanide complexed with acetonitrile as solvent gives good yields. Also, acetonitrile forms the part of solvent system, e.g. acetonitrile : toluene or acetonitrile: xylene. Thus, use of excessive dry xylene has been replaced by

mixture of acetonitrile and toluene/xylene in the ratio ranging from 1:6 to 1:3 and more preferably 1.2:6. Use of toluene helps to increase the reaction temperature. Also the use of potassium iodide is omitted. Due to this modification the demand on the reactor size is also lower. In another aspect cyclization of the intermediate (IV) (obtained by reacting acyl cyanide (III) with aminoguanidine bicarbonate) to form the heteroaromatic ring system of lamotrigine, can be carried out by using 0.5% to 1.5% aqueous KOH preferably 0.95% to 1.05% of aqueous KOH (as shown in reaction-3) instead of 10% methanolic KOH or only n-propanol, which are costly.

While the reaction of step (b) is carried out at room temperature, the preferred temperature range for reaction of step (a) is 40^0C to reflux temperature and that of cyclization of step (c) is 80^0C to reflux temperature.

With the help of this route of reaction, the yield of lamotrigine improves by around 5%.

In order to obtain lamotrigine of high grade purity, highly satisfactory impurity profile, white in color, free flowing, having lower moisture content, which can be efficiently and effectively dried and can be easily converted into pharmaceutical compositions, charcoalization in alcohol such as methanol was carried out.

PREPARATORY EXAMPLES

The invention is explained in detail in the following examples which are provided by way of illustrations only and should therefore not be construed to limit the scope of the invention.

Example 1

In a mixture of 128 gm. of copper cyanide, 120ml. of acetonitrile and 200 ml. of toluene, the solution of 200 gm. of 2,3-dichlorobenzoylchloride (II) in 250 ml of toluene was added. The reaction mixture was refluxed for 16 hour. After filtration, the solvent was removed under reduced pressure to give 200 ml of oily 2,3-dichlorobenzoyl cyanide (III).

Example 2

In the solution of 2.28 Kg. of sulphuric acid and 1.20 lit. of water was added 260 gm. aminoguanidinebicarbonate. To it added 2,3-dichlorobenzoyl cyanide i.e. compound - III (from Example - 1) in 800 ml. of acetonitrile and stirred for 60 hrs. Filtered the solid. The solid was further added to aqueous NaOH. The mixture was stirred for 1 hr. at pH 11-12. The material obtained after filtration i.e. compound - IV was used in Example - 3.

Example 3

Compound (IV), obtained from 2,3-dichlorobenzoyl cyanide (III) was refluxed in 1.5 lit. of 1% KOH solution for 1.5 hr to give white solid. It was filtered and washed with water to give 107 gm. of Lamotrigine.

m.p. : 216-218^{0}C

IR(KBr):3450, 3315, 1646, 1619, 1557, 1490, 792cm^{-1}

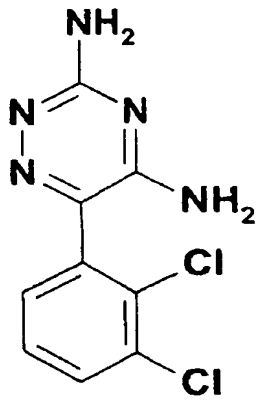
^{1}H NMR(DMSO, 400MHz)δ:7.61(d,1H,J=1.5Hz),7.35(t,1H,J=7.9Hz),

7.26(dxd,1H,J_1=1.6Hz,J_2=7.6Hz)

Mass : 256.4(100%)

I Claim :

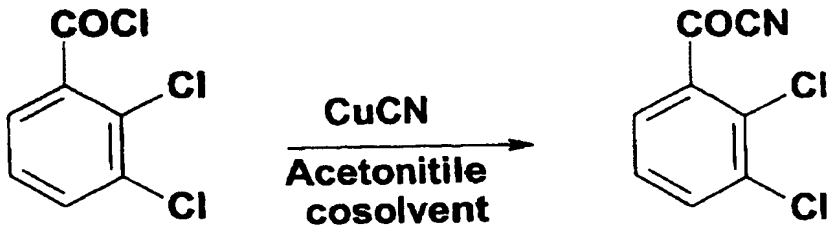
1. An improved process for the preparation of 3,5-diamino-6-(2,3-dichlorophenyl)-1,2,4-triazine of formula (I)



(I)

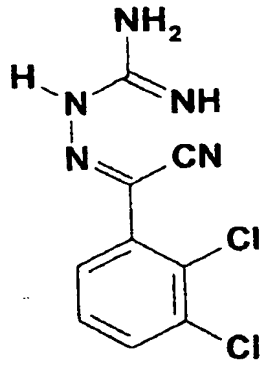
which process comprises the step of:

(a) reacting 2,3-dichlorobenzoylchloride of formula (II) with cuprous cyanide in presence of acetonitrile and a cosolvent to produce dichlorobenzoyl cyanide (III).



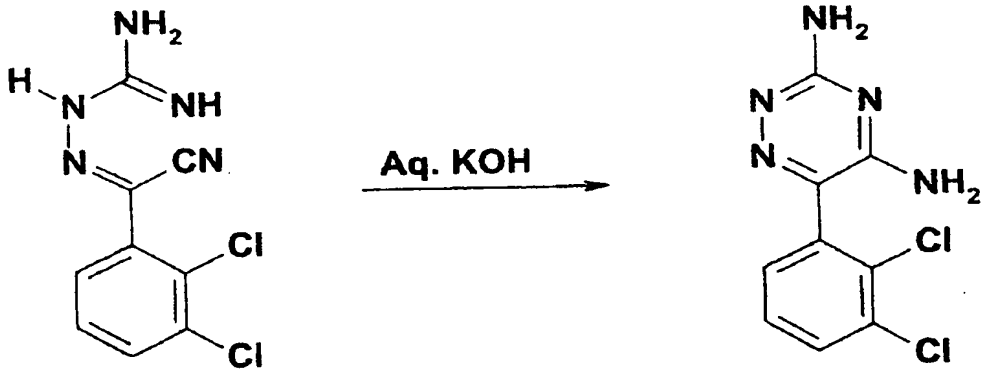
(II) (III)

(b) reacting said dichlorobenzoyl cyanide (III) obtained in step (a) with aminoguanidine bicarbonate to produce the intermediate product of formula (IV)



(IV)

(c) cyclizing said intermediate of formula (IV) in presence of aqueous potassium hydroxide to produce 3,5-diamino-6-(2,3-dichlorophenyl)-1,2,4-triazine.



(IV) (I)

2. The process as claimed in claim 1 wherein said reaction of step (a) is carried out at a temperature ranging from 40^0C to reflux temperature, said reaction of step (b) is

carried out at room temperature, and said cyclization of step (c) is carried out at a temperature ranging from 80^0C to reflux temperature.

3. A process as claimed in claim 1, wherein said cosolvent used in step (a) is toluene.

4. A process as claimed in claim 1 wherein said cosolvent used in step (a) is xylene.

5. A process as claimed in claim 1, 3 or 4, wherein the range of ratio of volumes of acetonitrile to cosolvent in step (a) is 1:6 to 1:3.

6. A process as claimed in claim 5, wherein said ratio of volumes of acetonitrile to cosolvent is 1.2:6.

7. A process as claimed in claim 1, wherein 0.95% to 1.05% aqueous KOH is used in cyclization.

8. The process as claimed in claim 1 wherein the product obtained by step (c) is further charcoalized in alcohol to obtain a high purity grade, free flowing white product with highly satisfactory impurity profile and low moisture content, which can be efficiently and effectively dried and can be easily converted into pharmaceutical compositions.

9. The process as claimed in claim 8 wherein the alcohol used for charcoalization is methanol.

INTERNATIONAL SEARCH REPORT

Inte Jonal Application No
PCT/IB 99/01955

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D253/06

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 4 602 017 A (SAWYER DAVID A ET AL) 22 July 1986 (1986-07-22) cited in the application example 1	1
Y	FR 2 741 879 A (ESTEVE LABOR DR) 6 June 1997 (1997-06-06) page 9, line 3 - line 4	1
Y	DE 27 08 183 A (DEGUSSA) 31 August 1978 (1978-08-31) page 5 -page 6; examples	1

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
4 February 2000	17/02/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	De Jong, B

2

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Information on patent family members

Inte. onal Application No
PCT/IB 99/01955

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 4602017 A	22-07-1986	AR 227521 A	15-11-1982
		AT 370097 B	25-02-1983
		AU 566870 B	05-11-1987
		AU 530999 B	04-08-1983
		AU 5890680 A	04-12-1980
		BG 60427 B	31-03-1995
		CA 1112643 A	17-11-1981
		CA 1133938 A	19-10-1982
		CS 234018 B	14-03-1985
		DD 151309 A	14-10-1981
		DK 233880 A,B,	02-12-1980
		EP 0021121 A	07-01-1981
		EP 0059987 A	15-09-1982
		ES 491998 A	16-05-1981
		FI 801758 A,B,	02-12-1980
		FI 840888 A,B,	06-03-1984
		GR 68380 A	28-12-1981
		HU 182086 B	28-12-1983
		IE 49823 B	25-12-1985
		IL 60201 A	31-05-1984
		IT 1147087 B	19-11-1986
		JP 1044706 B	29-09-1989
		JP 1567898 C	10-07-1990
		JP 56025169 A	10-03-1981
		JP 1044179 B	26-09-1989
		JP 1569585 C	10-07-1990
		JP 61033163 A	17-02-1986
		LT 2066 R	15-06-1993
		LV 5246 A	10-10-1993
		MX 9202962 A	01-07-1992
		MY 6285 A	31-12-1985
		NZ 193890 A	06-07-1984
		NZ 198159 A	09-11-1984
		PL 224633 A	13-02-1981
		SU 1055331 A	15-11-1983
		US 4486354 A	04-12-1984
		YU 145680 A	28-02-1983
		ZA 8003250 A	27-01-1982
		ZW 12980 A	06-01-1982
FR 2741879 A	06-06-1997	AU 1194397 A	27-06-1997
		WO 9720827 A	12-06-1997
		ES 2128960 A	16-05-1999
DE 2708183 A	31-08-1978	AT 356642 B	12-05-1980
		AT 392477 A	15-10-1979
		BE 855255 A	30-11-1977
		CH 627443 A	15-01-1982
		DD 130240 A	15-03-1978
		FR 2381747 A	22-09-1978
		GB 1527966 A	11-10-1978
		IL 52236 A	30-01-1981
		IT 1143580 B	22-10-1986
		JP 53105425 A	13-09-1978
		NL 7706159 A	29-08-1978
		US 4108877 A	22-08-1978
		US 4122116 A	24-10-1978